

78. (Amended) An isolated nucleic acid encoding a polypeptide consisting of a *hedgehog* [amino acid sequence]polypeptide which is at least 98 percent identical to either SEQ ID No: 17 or an N-terminal fragment thereof having a molecular weight of about 19 kD, which *hedgehog* [amino acid sequence]polypeptide binds to a *patched* protein or [regulates]promotes proliferation of testicular germ line cells.

79. (Amended) An isolated nucleic acid encoding a polypeptide comprising a *hedgehog* amino acid sequence which is at least 98 percent identical to SEQ ID No: 17, which *hedgehog* amino acid sequence binds to a *patched* protein or [regulates]promotes proliferation of testicular germ line cells.

REMARKS

Claims 1-35, 39-43, 47-49, 52-71, and 75-79 constitute the pending claims in the present application. Claims 35, 39, 40, 42, 43, 49, 52-54, 62-70, and 75-79 were elected with traverse, and Applicants will cancel non-elected claims upon notification of allowable subject matter. Applicants cancel claims 63, 65, and 67. Applicants respectfully request reconsideration in view of the following remarks. Issues raised by the Examiner will be addressed below in the order they appear in the prior Office Action. Applicants take this opportunity to extend our appreciation to the Examiner and his Supervisor for their courteous and helpful comments during a telephone interview on August 7, 2001.

1. Applicants note with appreciation the Examiner's receipt and acceptance of the request for a Continued Prosecution Application (CPA) filed 4/11/01.
2. Applicants acknowledge that claims 1-35, 39-43, 47-49, 52-71, and 75-79 are the pending claims in this application.
3. Applicants acknowledge that the amendments of 4/11/01 have been entered in full.

4. Applicants acknowledge that claims 1-34, 41, 47-48, 55-61 and 71 are drawn to a non-elected invention, such election having been made with traverse.

5. Applicants acknowledge that claims 35, 39, 40, 42, 43, 49, 52-54, 62-70, and 75-79 are currently under examination.

6. Applicants note with appreciation the Examiner's correction to the numbering of new claims 75-79. Applicants have corrected claim 35 to resolve the discrepancy between the proposed amendment and the marked-up version, as observed in the prior response.

7. Applicants note Examiner's acknowledgement of the change in inventorship, and that notice of this change has been forwarded to the Office of Initial Patent Examination (OIPE). The correct inventor on the current application is P. Jin.

8-9. Claims 35-43, 77, 78, and 79 are rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which the applicants regard as the invention. To expedite prosecution, Applicants have amended the claims to incorporate the Examiner's comments. Such amendments are not made in acquiescence of the rejection, and Applicants reserve the right to prosecute claims of similar or differing scope.

(a) Applicants' correction of the discrepancy between the clean and amended claim 35 of Paper 37 obviates this rejection.

(b) Applicants have amended claims 35 and 77-79 to more explicitly point out that a hedgehog polypeptide enhances proliferation of testicular germ cells. Support for the matter of

these claims is found in the specification which describes the experimental evidence establishing the effects of hedgehog polypeptides on testicular germ cells (page 40, lines 6-30). Applicants maintain that one of skill in the art would recognize that the phrase “promotes proliferation of testicular germ cells” refers to the ability of a hedgehog polypeptide to act as a mitogen and increase the mitotic index of cell types of the developing testes, and thus the metes and bounds of the claimed subject matter can be readily determined.

(c) Applicants traverse this rejection. The Examiner points out that the “measured molecular weight value of a protein varies with the method by which it is measured.” Applicants point out, however, that such values do not vary widely or erratically, and this is one reason that the claimed subject matter is defined in terms of an approximate molecular weight value. In addition, even commonly used methods for measuring molecular weight values such as gel filtration chromatography and electrophoresis provide only an estimate of that molecular weight, and are still subject to variation based on the exact conditions used (see Guide to Protein Purification, Methods in Enzymology, Murray P. Deutscher ed., volume 182, 579-583, included herewith as Exhibit 1). Because of the inherent imprecision in their measurement, the art at the time of filing routinely described the molecular weight of proteins in terms of an approximate value, i.e., by using words like “about” or “approximately”. Applicants point out that claim language cannot be assessed in isolation, but must be analyzed with respect to the prior art and the interpretation of one of skill in the art (MPEP 2173.02). Since Applicants have defined the claimed subject matter in terms consistent with the standard language used in this field at the time of filing, Applicants maintain that one of skill in the art would be able to determine the metes and bounds of the claimed invention. Accordingly, reconsideration and withdrawal of this rejection is requested.

(d) Applicants have cancelled this claim rendering the rejection moot.

(e) Applicants traverse this rejection. The Examiner is directed to MPEP 2111.03 regarding the use of transitional phrases. “The transitional phrase ‘consisting essentially of’ limits the scope of a claim to the specified materials or steps ‘and those that do not materially affect the basic and novel characteristic(s) of the claimed invention.” *In re Herz*. The interpretation of the phrase ‘consisting essentially of’ is not a matter of debate. MPEP 2111.03

provides clear guidance that “[f]or search and examination purposes, absent a clear indication in the specification of what the basic and novel characteristics actually are, ‘consisting essentially of’ will be construed as equivalent to ‘comprising’.” Accordingly, the use of the phrase ‘consisting essentially of’ is not indefinite, but has a well defined and generally understood interpretation for search and examination purposes. Reconsideration and withdrawal of this rejection is requested.

10-11. Claims 35, 39, 40, 42, 43, 49, 52, 53, 54, 62, 63, 64, 65, 69, 70, and 75-79 are rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, specifically for failing to enable for polynucleotides encoding variants of SEQ ID No: 17. Applicants respectfully traverse this rejection.

The construction of polynucleotides encoding any desired polypeptide sequence is routinely practiced by one of skill in the art. The degenerate triplet genetic code is universally understood, and allows one to construct a given polypeptide sequence using any one of a number of polynucleotide variations. For example, given the polypeptide sequence Phe-Met-Phe, one of skill would recognize that this polypeptide can be encoded by any of the following polynucleotide sequences: UUU-AUG-UUU, UUC-AUG-UUU, UUU-AUG-UUC, or UUC-AUG-UUC. Although generally understood, this principle was also reviewed in detail in the specification (page 12, lines 24-30).

The making of polypeptide variants is routinely practiced in the art using common and simple laboratory techniques. Such substitutions are made based on both the sequence data, and on knowledge of the structure of the twenty amino acids. Amino acid substitutions can be chosen in order to maintain or disrupt the shape and charge density of a region of the protein, and one of skill in the art would recognize that the choice of an amino acid substitution that would either maintain or disrupt a given region of a protein is highly predictable based on the structure of the twenty natural amino acids. For example, arginine and lysine are positively charged amino acids and the substitution of one for the other is routinely practiced by those of skill in the

art without affecting the function of the overall sequence. Similarly, the substitution of a leucine for an isoleucine residue is routinely practiced without affecting the function of the protein (reviewed in detail in specification, page 14, Table 1). Additionally, one of skill in the art is also guided by the known sequences and the conserved structure of other hedgehog proteins from a variety of species including fish, *Xenopus*, chick, and mouse. For example, the mouse Desert hedgehog is very highly related to human Desert hedgehog, and comparisons between these sequences would inform the skilled artisan as to several sites amenable to amino acid substitution without any change in the structure or function of the resulting polypeptide variant. The wealth of sequence information available for hedgehog family members, including the very highly related mouse Desert hedgehog, would guide one of skill in the art in the making of polypeptide variants by identifying residues where even non-conservative amino acid substitutions would be tolerated.

However, the art at the time of filing no longer relied upon purely rational choices of conserved amino acid substitutions to construct polypeptide variants. The fields of combinatorial and scanning mutagenesis had trivialized the once complex and painstaking process of making and testing polypeptide variants long before the filing of the present application (for examples see Reidhaar-Olson and Sauer, 1988; Wissmann et al., 1991; Delagrave et al., 1993 enclosed herewith as Exhibits 2-4). These techniques were routinely practiced, and allow a wide range of amino acid substitutions to be made and tested for the maintenance or disruption of functional properties without undue experimentation. The making and using of such polypeptide variants was clearly enumerated in the specification which contemplates functionally related proteins and peptides that either maintain or disrupt hedgehog activity (page 14, lines 4-8; page 15). Additionally, the specification reviews the methods commonly employed to synthesis peptides and peptide variants including solid phase chemical synthesis and recombinant DNA methods (page 18, lines 4-30). All of these methods are commonly practiced, and their use requires no undue experimentation on the part of one of skill in the art.

Applicants further note that the claimed subject matter is defined by specific functional properties. Therefore, one of skill in the art is guided with extremely specific criteria with which to evaluate variant peptides synthesized by the above methods. Furthermore, the claimed variant

peptides differ by only 2% from the recited peptide. This limits the number of possible variants, and also limits the number of substitutions included in any one variant. These factors further simplify and guide one of skill in art in the process of making and testing variants. Accordingly, one of skill in the art faced with the task of constructing variants differing by 2% or less and possessing defined functional properties would not expect to expend any more effort than normally required. Once the polypeptide sequences are chosen, the construction of the corresponding polynucleotide sequences is trivial. Thus, Applicants submit that the claimed subject matter is enabled throughout its scope.

Claims 35, 39, 40, 42, 43, 49, 52, 53, 54, and 77-79 are similarly rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. To expedite prosecution, Applicants have amended the claims in accordance with the Examiner's suggestion such that the claims require that a patched protein bind a hedgehog polypeptide. Such amendments are not made in acquiescence of the rejection, and Applicants reserve the right to prosecute claims of similar or differing scope. Reconsideration and withdrawal of this rejection is requested.

Claim 64 was similarly rejected under 35 U.S.C. §112, first paragraph. Applicants' amendments to claim 64 obviate this rejection.

12. Claims 63, 65, 67, 69, and 70 are rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention, specifically that Applicants' did not have possession of variants of the claimed polypeptides. Applicants have cancelled claim 63 rendering the rejection moot. Applicants reserve the right to prosecute claims of similar or differing scope.

13. Applicants note with appreciation the withdrawal of the previous rejection of claims 63 and 67 under U.S.C. 102(b) as being anticipated by Hillier et al.

14. Applicants traverse the objection to claims 66 and 68, and request their reconsideration as written in light of the amendments to the pending claims.

CONCLUSION

In view of the foregoing amendments and remarks, Applicants submit that the pending claims are in condition for allowance. Early and favorable reconsideration is respectfully solicited. The Examiner may address any questions raised by this submission to the undersigned at 617-951-7000. Should an extension of time be required, Applicants hereby petition for same and request that the extension fee and any other fee required for timely consideration of this submission be charged to **Deposit Account No. 18-1945**.

Date: August 7, 2001

Customer No: 28120
Docketing Specialist
Ropes & Gray
One International Place
Boston, MA 02110

Respectfully Submitted,



David P. Halstead
Reg. No. 44,735